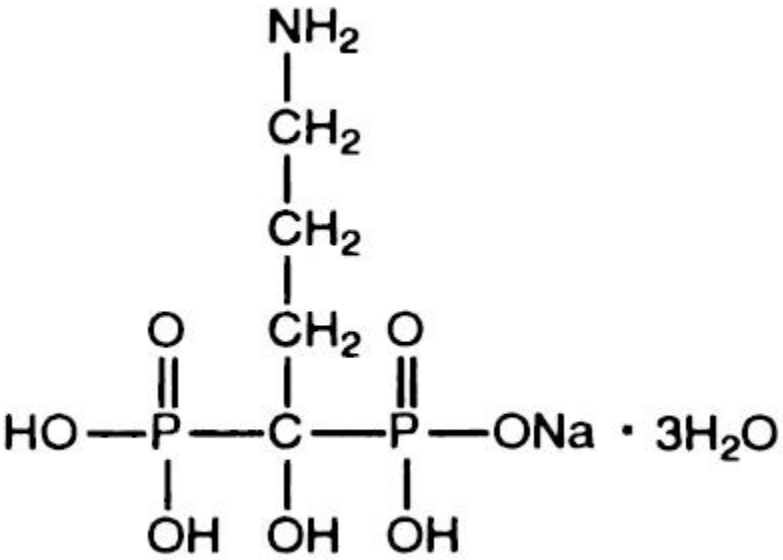
ALENDRONATE SODIUM - alendronate sodium tablet
TEVA Pharmaceuticals USA Inc

DESCRIPTION

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.
Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.
The structural formula is:



$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ M.W. 325.12
Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.
Each tablet, for oral administration contains 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.
Alendronate sodium tablets USP meet USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10 fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption
Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution
Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism
There is no evidence that alendronate is metabolized in animals or humans.

Excretion
Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric
The oral bioavailability in children was similar to that observed in adults; however, alendronate sodium is not indicated for use in children (see **PRECAUTIONS**, **Pediatric Use**).

Gender
Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric
Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION**).

Race
Pharmacokinetic differences due to race have not been studied.

Renal insufficiency
Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **Alendronate sodium is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic insufficiency
As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions
(Also see **PRECAUTIONS**, **Drug Interactions**.)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics
Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women
Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50 fold and the risk of vertebral fracture 15 to 30 fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate sodium 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies alendronate sodium 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis and once weekly alendronate sodium 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate sodium 5 mg/day. In one-year studies with once weekly alendronate sodium 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men
Treatment of men with osteoporosis with alendronate sodium 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Glucocorticoid-Induced Osteoporosis
Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's Disease of Bone
Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

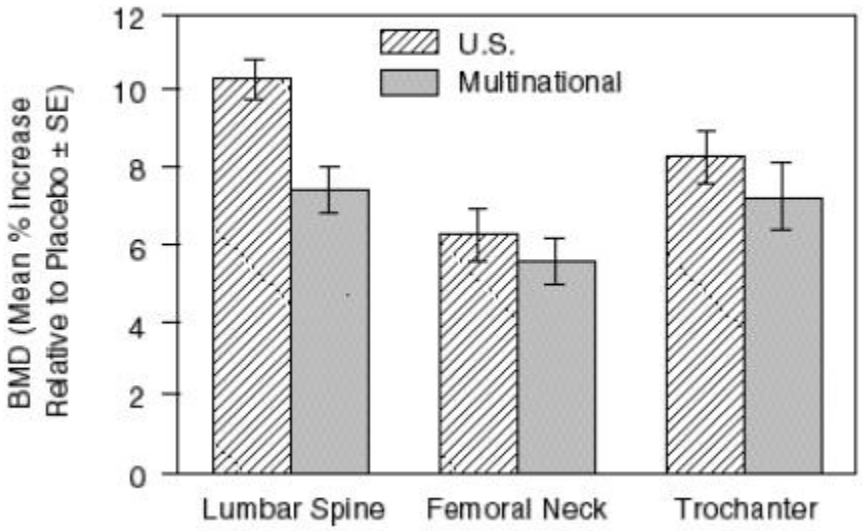
Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

Alendronate sodium decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate sodium 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate sodium induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of Osteoporosis in Postmenopausal Women

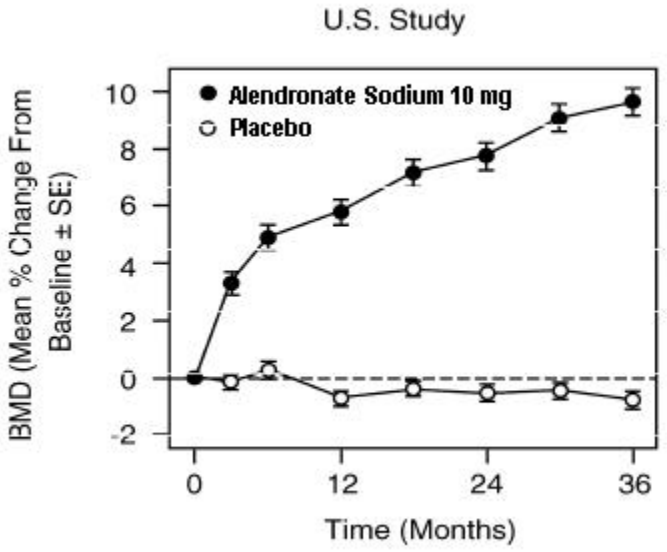
Effect on bone mineral density
The efficacy of alendronate sodium 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 10 mg/day relative to placebo-treated patients at three years for each of these studies.



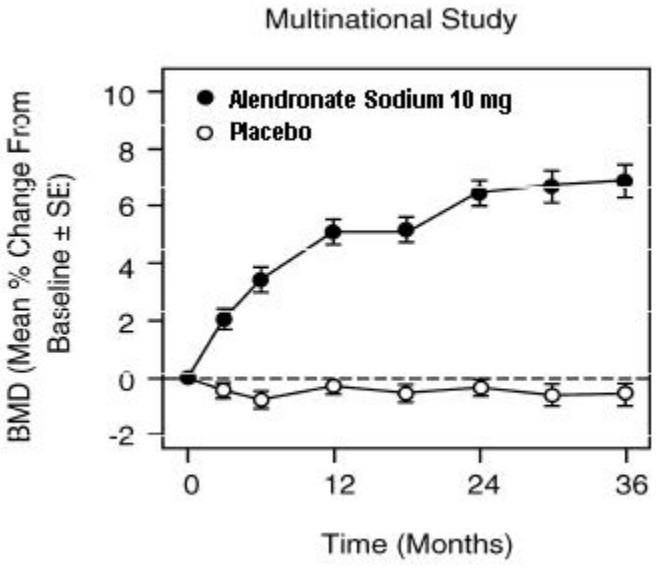
Osteoporosis Treatment Studies in Postmenopausal Women Increase in BMD Alendronate Sodium 10 mg/day at Three Years

At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate sodium 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with alendronate sodium 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%).

BMD at the femoral neck, forearm and total body were maintained. Alendronate sodium was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean). Thus, overall alendronate sodium reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.



Osteoporosis Treatment Studies in Postmenopausal Women



Time Course of Effect of Alendronate Sodium 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline

In patients with postmenopausal osteoporosis treated with alendronate sodium 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with alendronate sodium is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly alendronate sodium 70 mg (n = 519) and alendronate sodium 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once-weekly group (n = 440) and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group (n = 330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of alendronate sodium on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of alendronate sodium on the incidence of vertebral fractures (detected by digitized radiography; approximately one-third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate sodium (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with alendronate sodium experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received alendronate sodium had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027 patient study (alendronate sodium, n = 1022; placebo, n = 1005) demonstrated that treatment with alendronate sodium resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

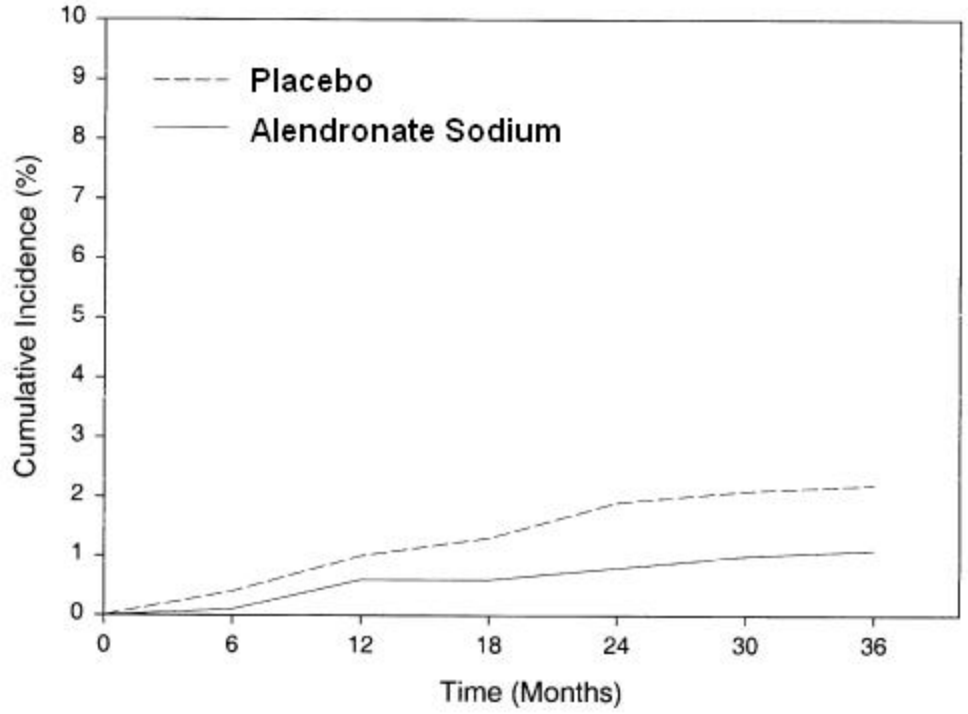
Effect of Alendronate Sodium on Fracture Incidence in the Three-Year Study of FIT (Patients With Vertebral Fracture at Baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1022)	Placebo (n = 1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)*				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47†
≥ 2 new vertebral fracture	0.5	4.9	4.4	90†
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26‡
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54§
Hip fracture	1.1	2.2	1.1	51¶
Wrist (forearm) fracture	2.2	4.1	1.9	48¶

*Number evaluable for vertebral fractures: Alendronate sodium, n = 984; placebo, n = 966
†$p < 0.001$
‡$p = 0.007$
§$p < 0.01$
¶$p < 0.05$

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate sodium significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on alendronate sodium, $p = 0.047$. The figure below displays the cumulative incidence of hip fractures in this study.



Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT (Patients With Radiographic Vertebral Fracture at Baseline)

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture
This randomized, double-blind, placebo-controlled, 4432-patient study (alendronate sodium, n = 2214; placebo, n = 2218) further investigated the reduction in fracture incidence due to alendronate sodium. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of Alendronate Sodium on Fracture Incidence in Osteoporotic[*] Patients in the Four-Year Study of FIT (Patients Without Vertebral Fracture at Baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1545)	Placebo (n = 1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48[‡]
≥ 2 new vertebral fracture	0.1	0.6	0.5	78[§]
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22[¶]
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)[#]
Hip fracture	1.0	1.4	0.4	29 (NS)[#]
Wrist (forearm) fracture	3.9	3.8	-0.1	NS[#]

*Baseline femoral neck BMD at least 2 SD below the mean for young adult women
†Number evaluable for vertebral fractures: Alendronate sodium, n = 1426; placebo, n = 1428
‡$p < 0.001$
§$p = 0.035$
¶$p = 0.01$
#Not significant. This study was not powered to detect differences at these sites.

Fracture results across studies
In the Three-Year Study of FIT, alendronate sodium reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, $p < 0.001$); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, $p = 0.001$); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, $p = 0.034$).

Alendronate sodium reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, $p < 0.001$) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, $p < 0.001$) in the Three-Year Study of FIT. In the Four-Year Study of FIT, alendronate sodium reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, $p = 0.035$).

Thus, alendronate sodium reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

Alendronate sodium, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone Histology
Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate sodium at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with alendronate is of normal quality.

Men
The efficacy of alendronate sodium in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

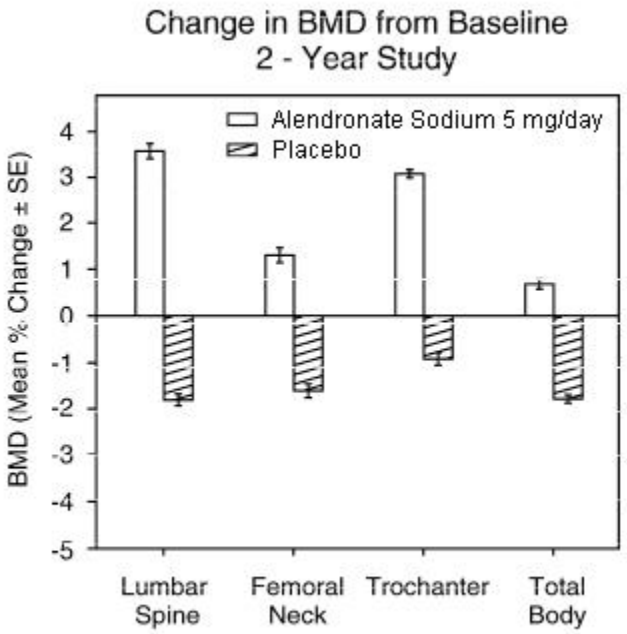
A two-year, double-blind, placebo-controlled, multicenter study of alendronate sodium 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving alendronate sodium 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with alendronate sodium also reduced height loss (alendronate sodium, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly alendronate sodium 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, 2) a BMD T-score ≤ -2 at the lumbar spine and ≤ -1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving alendronate sodium 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

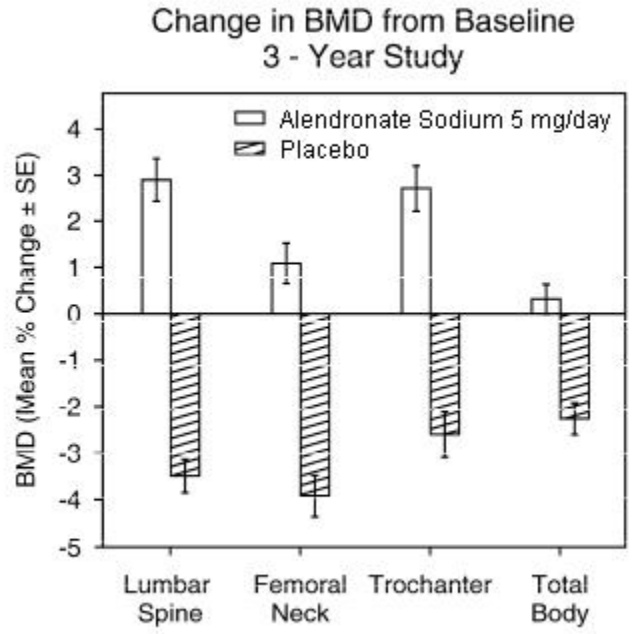
In both studies, BMD responses were similar regardless of age (≥ 65 years vs. < 65 years), gonadal function (baseline testosterone < 9 ng/dL vs. ≥ 9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤ -2.5 vs. > -2.5).

Prevention of Osteoporosis in Postmenopausal Women
Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40 to 60 years of age. One thousand six hundred nine patients (alendronate sodium 5 mg/day; n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate sodium 5 mg/day; n = 88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate sodium 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, alendronate sodium 5 mg/day reduced the rate of bone loss at the forearm

by approximately half relative to placebo. Alendronate sodium 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.



Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly alendronate sodium 35 mg (n = 362) and alendronate sodium 5 mg daily (n = 361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35 mg once-weekly group (n = 307) and 3.2% (2.9, 3.5%; 95% CI) in the 5 mg daily group (n = 298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone Histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate sodium at doses of up to 10 mg/day.

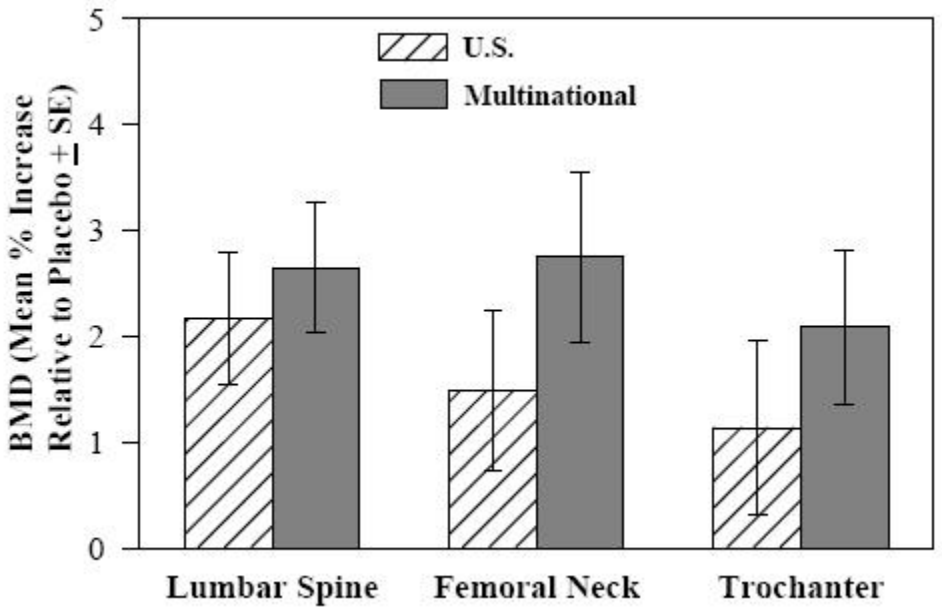
Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)
The effects on BMD of treatment with alendronate sodium 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n = 425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate sodium alone (both 6.0%).

The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n = 428). The addition of alendronate sodium 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with alendronate sodium and HRT, 94% on alendronate sodium alone, and 78% on HRT alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-Induced Osteoporosis
The efficacy of alendronate sodium 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included alendronate sodium 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 5 mg/day for each study.



Studies in Glucocorticoid – Treated Patients Increase in BMD Alendronate Sodium 5 mg/day at One Year

After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate sodium 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate sodium 5 mg/day. The increases in BMD with alendronate 10 mg/day were similar to those with alendronate sodium 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with alendronate sodium 10 mg/day were greater than those with alendronate sodium 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate sodium was effective regardless of dose or duration of glucocorticoid

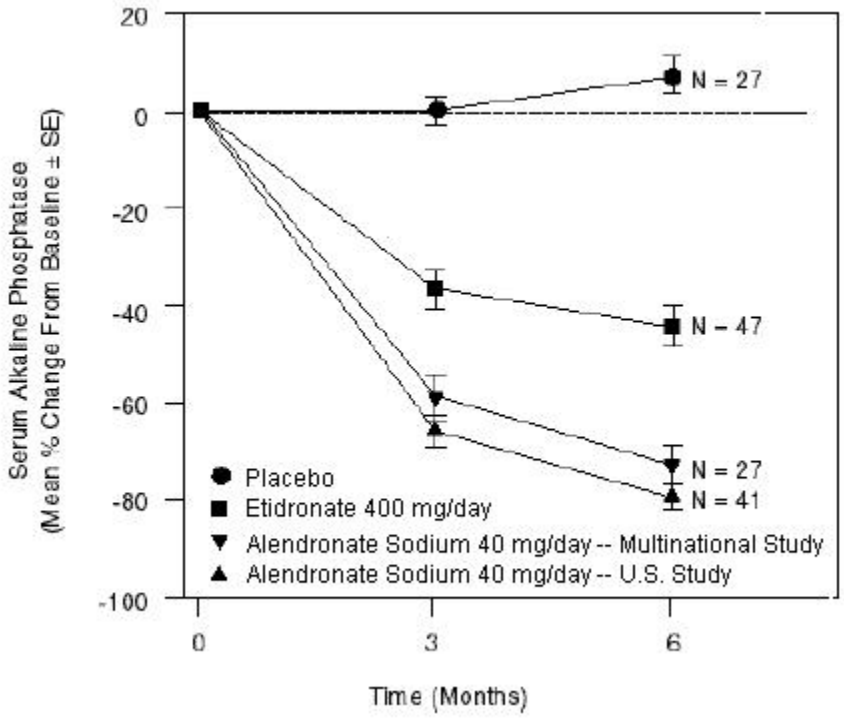
use. In addition, alendronate sodium was similarly effective regardless of age (< 65 vs. ≥ 65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate sodium at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate sodium 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate sodium 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate sodium (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate sodium 0.7% vs. placebo 6.8%).

Paget's Disease of Bone
The efficacy of alendronate sodium 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



Studies in Paget's Disease of Bone Effect on Serum Alkaline Phosphatase of Alendronate Sodium 40 mg/day Versus Placebo or Etidronate 400 mg/day

At six months the suppression in alkaline phosphatase in patients treated with alendronate sodium was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥ 60%) occurred in approximately 85% of patients treated with alendronate sodium in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. Alendronate sodium was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with alendronate sodium 40 mg/day for 6 months. As in patients treated for osteoporosis (see **Clinical Studies**, *Treatment of Osteoporosis in Postmenopausal Women*, Bone Histology), alendronate sodium did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal

lamellar bone was produced during treatment with alendronate sodium, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with alendronate sodium is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000 fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

Alendronate sodium tablets are indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
- For the treatment of osteoporosis, alendronate sodium tablets increase bone mass and reduce the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture (see **CLINICAL PHARMACOLOGY**, **Pharmacodynamics**).
- For the prevention of osteoporosis, alendronate sodium tablets may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture. Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of alendronate sodium for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis

- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see **PRECAUTIONS**, Glucocorticoid-induced osteoporosis). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

- Treatment of Paget's disease of bone in men and women
- Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia

- Inability to stand or sit upright for at least 30 minutes

- Hypersensitivity to any component of this product

- Hypocalcemia (see **PRECAUTIONS**, **General**)

WARNINGS

Alendronate sodium, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see **DOSAGE AND ADMINISTRATION**). In patients who cannot comply with dosing instructions due to mental disability, therapy with alendronate sodium should be used under appropriate supervision.

Because of possible irritant effects of alendronate sodium on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been postmarketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.
Hypocalcemia must be corrected before initiating therapy with alendronate sodium (see **CONTRAINDICATIONS**). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium.
Presumably due to the effects of alendronate sodium on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.
Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain
In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). This category of drugs includes alendronate sodium. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

Dental
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., preexisting dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency
Alendronate sodium is not recommended for patients with renal insufficiency (creatinine clearance < 35 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Glucocorticoid-induced osteoporosis
The risk versus benefit of alendronate sodium for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see **INDICATIONS AND USAGE**). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined alendronate sodium and glucocorticoid treatment.

The efficacy of alendronate sodium for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of alendronate sodium has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of alendronate sodium beyond two years has not been studied.

The efficacy of alendronate sodium in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General
Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions
Patients should be instructed that the expected benefits of alendronate sodium may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate sodium (see **CLINICAL PHARMACOLOGY, Pharmacokinetics,** *Absorption*).
To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with a full glass of water (6 to 8 oz). Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium and consult their physician.
Patients should be instructed that if they miss a dose of once weekly alendronate sodium, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions
(Also see **CLINICAL PHARMACOLOGY, Pharmacokinetics,** *Drug Interactions*.)

Estrogen/Hormone Replacement Therapy (HRT)
Concomitant use of HRT (estrogen ± progestin) and alendronate sodium was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see **CLINICAL PHARMACOLOGY**, **Clinical Studies**, *Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)* and **ADVERSE REACTIONS**, **Clinical Studies**, Concomitant use with estrogen/hormone replacement therapy).

Calcium Supplements/Antacids
It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate sodium. Therefore, patients must wait at least one-half hour after taking alendronate sodium before taking any other oral medications.

Aspirin
In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of alendronate sodium greater than 10 mg and aspirin-containing products.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Alendronate sodium may be administered to patients taking NSAIDs. In a 3 year, controlled, clinical study (n = 2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate sodium 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate sodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice ($p = 0.003$) in a 92 week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.
Parafollicular cell (thyroid) adenomas were increased in high-dose male rats ($p = 0.003$) in a 2 year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.
Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Teratogenic Effects

Pregnancy category C
Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. Alendronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium is administered to nursing women.

Pediatric Use
The efficacy and safety of alendronate sodium were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4 to 18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg alendronate sodium daily (weight < 40 kg) or 10 mg alendronate sodium daily (weight ≥ 40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the alendronate sodium-treated patients and 0.1 in the placebo-treated patients. Treatment with alendronate sodium did not reduce the risk of fracture. Sixteen percent of the alendronate sodium patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In alendronate sodium-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the alendronate sodium and placebo groups in reduction of bone pain.
Alendronate sodium tablets are not indicated for use in children. (For clinical adverse experiences in children, see **ADVERSE REACTIONS**, **Clinical Studies**, *Osteogenesis Imperfecta*.)

Geriatric Use

Of the patients receiving alendronate sodium in the Fracture Intervention Trial (FIT), 71% (n = 2302) were ≥ 65 years of age and 17% (n = 550) were ≥ 75 years of age. Of the patients receiving alendronate sodium in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see **CLINICAL PHARMACOLOGY, Clinical Studies**), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of Osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n = 994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n = 6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49 to 54% had a history of gastrointestinal disorders at baseline and 54 to 89% used non-steroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (n = 196)	Placebo % (n = 397)	Alendronate Sodium† % (n = 3236)	Placebo % (n = 3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle, or joint) pain	4.1	2.5	0.4	0.3

muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

*****10 mg/day for three years
†5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of alendronate sodium in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of alendronate sodium in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Once Weekly Alendronate Sodium 70 mg % (n = 519)	Alendronate Sodium 10 mg/day % (n = 370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2

muscle cramp	0.2	1.1

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium 10 mg/day and a one-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 2% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 2% of Patients

	Two-Year Study		One-Year Study	
	Alendronate Sodium 10 mg/day % (n = 146)	Placebo % (n = 95)	Once Weekly Alendronate Sodium 70 mg % (n = 109)	Placebo % (n = 58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of Osteoporosis in Postmenopausal Women

The safety of alendronate sodium 5 mg/day in postmenopausal women 40 to 60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate sodium for either two or three years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Two/Three-Year Studies		One-Year Study	
	Alendronate Sodium 5 mg/ day	Placebo %	Alendronate Sodium 5 mg/day	Once Weekly Alendronate Sodium

	% (n = 642)	(n = 648)	% (n = 361)	35 mg % (n = 362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy
In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n = 853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n = 354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis
In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in the following table:

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Alendronate Sodium 10 mg/day % (n = 157)	Alendronate Sodium 5 mg/day % (n = 161)	Placebo % (n = 159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3

constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n = 147) was consistent with that observed in the first year.

Paget's Disease of Bone
In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3 to 12 months were similar to those in postmenopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta
Alendronate sodium tablets are not indicated for use in children.

The overall safety profile of alendronate sodium in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with alendronate sodium. However, there was an increased occurrence of vomiting in OI patients treated with alendronate sodium compared to placebo. During the 24 month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with alendronate sodium and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of alendronate sodium 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including alendronate sodium (see **ADVERSE REACTIONS**, *Postmarketing Experience*, *Body as a Whole*).

Laboratory Test Findings
In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Postmarketing Experience
The following adverse reactions have been reported in postmarketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate sodium, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see **WARNINGS; PRECAUTIONS, Information for Patients**, and **DOSAGE AND ADMINISTRATION**).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see **PRECAUTIONS**, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see **PRECAUTIONS**, *Musculoskeletal Pain*); joint swelling.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with alendronate sodium. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

Alendronate sodium tablets must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see **PRECAUTIONS, Information for Patients**). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate sodium tablets (see **PRECAUTIONS, Drug Interactions**). Waiting less than 30 minutes, or taking alendronate sodium tablets with food, beverages (other than plain water) or other medications will lessen the effect of alendronate sodium tablets by decreasing its absorption into the body.

Alendronate sodium tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an alendronate sodium tablet should be swallowed with a full glass of water (6 to 8 oz). Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see **WARNINGS; PRECAUTIONS, Information for Patients**).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see **PRECAUTIONS, General**).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendronate sodium tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Treatment of Osteoporosis in Postmenopausal Women

(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Treatment to Increase Bone Mass in Men With Osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Prevention of Osteoporosis in Postmenopausal Women

(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with alendronate sodium has been studied for up to 7 years.

Treatment of Glucocorticoid-Induced Osteoporosis in Men and Women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's Disease of Bone in Men and Women
The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's Disease
In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate sodium tablets. Specific retreatment data are not available, although responses to alendronate sodium tablets were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with alendronate sodium tablets may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED
Alendronate sodium tablets USP, for oral administration, are available as:
5 mg – white to off-white, round flat-faced beveled-edge, unscored tablet debossed with "93" on one side and "5140" on the other side, in bottles of 30 and 100.
10 mg – white to off-white, round, convex, unscored tablet debossed with "93" on one side and "5141" on the other side, in bottles of 30 and 100.
35 mg – white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5172" on the other side, in unit-of-use blister package of 4 and unit dose packages of 20 (2 x 10).
40 mg – white to off-white, oval convex, unscored tablet debossed with "93" on one side and "5142" on the other side, in bottles of 30.
70 mg – white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5171" on the other side, in unit-of-use blister package of 4 and unit dose packages of 20 (2 x 10).
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Rev. F 7/2009

PATIENT INFORMATION
ONCE DAILY ALENDRONATE SODIUM TABLETS USP
Rx only
Read this information before you start taking alendronate sodium tablets USP. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss alendronate sodium tablets USP when you start taking your medicine and at regular checkups.
What is the most important information I should know about alendronate sodium tablets USP?
- **You must take alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take alendronate sodium tablets USP?".)**

- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?
Alendronate sodium tablets USP are a prescription medicine for:
- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).

- Treatment to increase bone mass in men with osteoporosis.

- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.
Alendronate sodium tablets USP are not hormones.
There is more information about osteoporosis at the end of this leaflet.
Who should not take alendronate sodium tablets USP?
Do not take alendronate sodium tablets USP if you:
- Have certain problems with your esophagus, the tube that connects your mouth with your stomach

- Cannot stand or sit upright for at least 30 minutes

- Have low levels of calcium in your blood

- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?
Tell your doctor about all of your medical conditions, including if you:
- **have problems with swallowing**

- **have stomach or digestive problems**

- **have kidney problems**

- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.

- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.
How should I take alendronate sodium tablets USP?
- Take 1 alendronate sodium tablet USP once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.

- Take alendronate sodium tablets USP while you are sitting or standing.

- Swallow your alendronate sodium tablet USP with a full glass (6 to 8 oz) of plain water only.

Do **not** take alendronate sodium tablets USP with:
Mineral water
Coffee or tea
Juice
Alendronate sodium tablets USP work only if taken on an empty stomach.
Do not chew or suck on an alendronate sodium tablet USP.
After swallowing your alendronate sodium tablet USP, wait at least 30 minutes:
- before you lie down. You may sit, stand or walk, and do normal activities like reading.

- before you take your first food or drink except for plain water.

- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after first food of the day.
- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?
- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.

- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?
- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.

- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.

- Do not lie down for at least 30 minutes **after** taking alendronate sodium tablets USP. Do not lie down until **after** your first food of the day.

What are the possible side effects of alendronate sodium tablets USP?
Alendronate sodium tablets USP may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "**What is the most important information I should know about alendronate sodium tablets USP?**".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with alendronate sodium tablets USP or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking alendronate sodium tablets USP and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
- **Chest pain**
- **New or worsening heartburn**
- **Trouble or pain when swallowing**

- Esophagus problems may get worse if you continue to take alendronate sodium tablets USP.

- Mouth sores (ulcers) may occur if the alendronate sodium tablets USP are chewed or dissolved in the mouth.

- You may get flu-like symptoms typically at the start of treatment with alendronate sodium tablets USP.

- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

- Alendronate sodium tablets USP may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.

- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, hair loss, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.

- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.
These are not all the side effects with alendronate sodium tablets USP. Ask your doctor or pharmacist for more information.

How do I store alendronate sodium tablets USP?

- Store alendronate sodium tablets USP at room temperature, 68º to 77°F (20º to 25°C).

- Safely discard alendronate sodium tablets USP that are out-of-date or no longer needed.

- **Keep alendronate sodium tablets USP and all medicines out of the reach of children.**

General information about using alendronate sodium tablets USP safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use alendronate sodium tablets USP for a condition for which they were not prescribed. Do not give alendronate sodium tablets USP to other people, even if they have the same symptoms you have. It may harm them.
Alendronate sodium tablets USP are not indicated for use in children.
This leaflet is a summary of information about alendronate sodium tablets USP. If you have any questions or concerns about alendronate sodium tablets USP or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about alendronate sodium tablets USP written for health care providers. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in alendronate sodium tablets USP?

Alendronate sodium tablets USP contain alendronate sodium as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.
Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.
At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:
Women who:

- Are going through or who are past menopause

Men who:
- Are elderly

People who:
- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?
In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:
- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Rev. A 10/2008

PATIENT INFORMATION
ONCE WEEKLY ALENDRONATE SODIUM TABLETS USP
Rx only
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What is the most important information I should know about once weekly alendronate sodium tablets USP?
- **You must take once weekly alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take once weekly alendronate sodium tablets USP?".)**
- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?
Alendronate sodium tablets USP are a prescription medicine for:
- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- Alendronate sodium tablets USP are for treatment and prevention of osteoporosis.

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.
Alendronate sodium tablets USP are not hormones.
There is more information about osteoporosis at the end of this leaflet.

Who should not take alendronate sodium tablets USP?
Do not take alendronate sodium tablets USP if you:
- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?
Tell your doctor about all of your medical conditions, including if you:
- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.
- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.
How should I take once weekly alendronate sodium tablets USP?
- Choose the day of the week that best fits your schedule.
- Take 1 dose of alendronate sodium tablets USP every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take alendronate sodium tablets USP while you are sitting or standing.
- Take your alendronate sodium tablets USP with plain water only as follows:
- Swallow one tablet with a full glass (6 to 8 oz) of plain water.

Do **not** take alendronate sodium tablets USP with:
Mineral water
Coffee or tea
Juice
Alendronate sodium tablets USP work only if they are taken on an empty stomach.
Do not chew or suck on an alendronate sodium tablet USP.
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- before you lie down. You may sit, stand or walk, and do normal activities like reading.
- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after your first food of the day.
- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?
- If you miss a dose, take only 1 dose of alendronate sodium tablets USP on the morning after you remember. Do not take 2 doses on the same day. Continue your usual schedule of 1 dose once a week on your chosen day.
- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?
- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.

- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.

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How do I store alendronate sodium tablets USP?
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mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.
At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

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Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:
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- Are going through or who are past menopause

Men who:

- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:

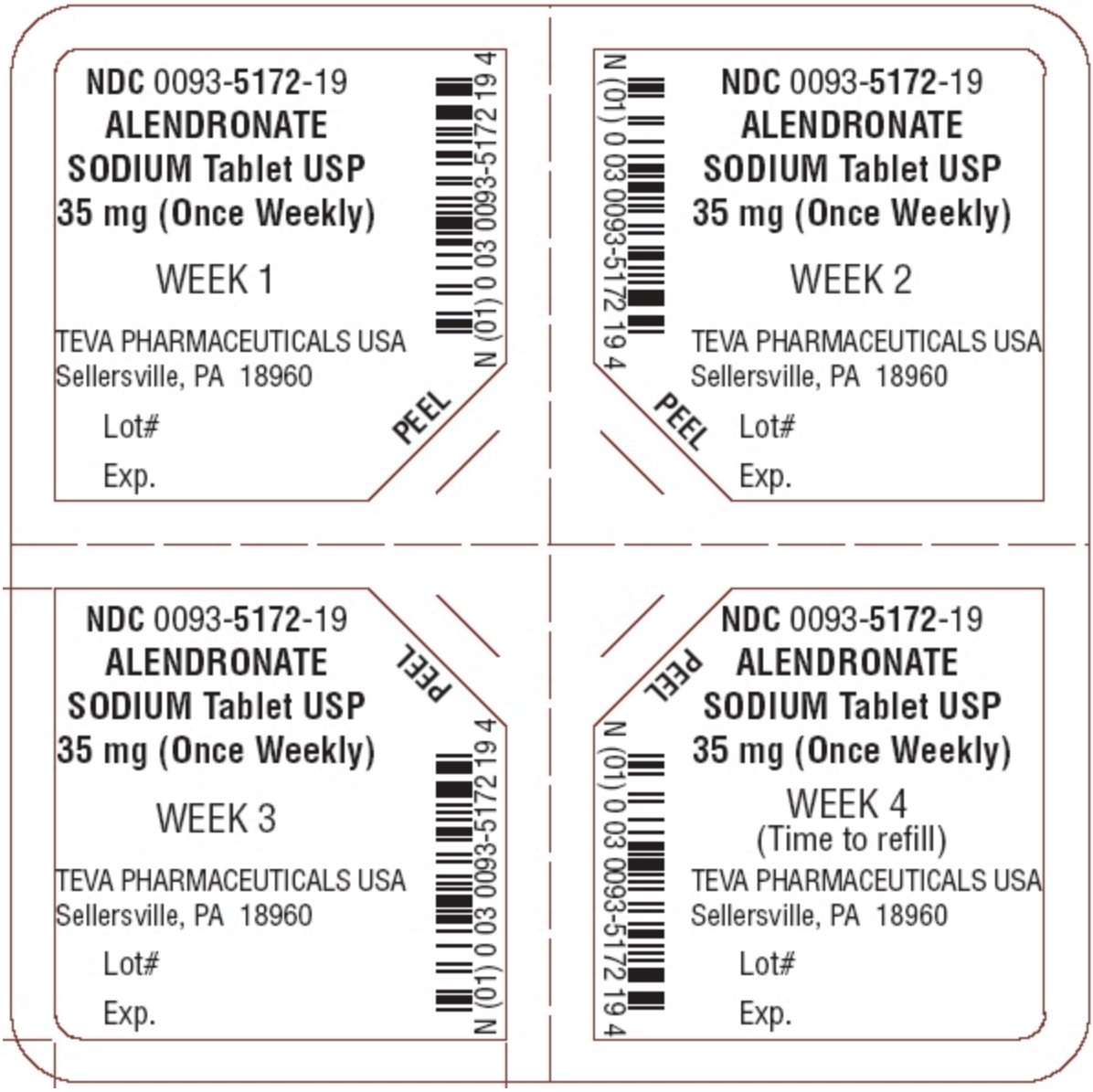
- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Rev. A 10/2008

PRINCIPAL DISPLAY PANELS

5 mg Label - 30 Tablets Text
NDC 0093-**5140**-56
ALENDRONATE
SODIUM
Tablets USP
5 mg*
***Each tablet contains 6.53 mg alendronate sodium (5 mg free acid equivalent).
Rx only
30 TABLETS
TEVA

10 mg Label - 30 Tablets Text
NDC 0093-**5141**-56
ALENDRONATE
SODIUM
Tablets USP
10 mg*
***Each tablet contains 13.05 mg alendronate sodium (10 mg free acid equivalent).
Rx only
30 TABLETS
TEVA



35 mg Blister Card - 4 Tablets Text
NDC 0093-**5172**-19
ALENDRONATE
SODIUM Tablet USP
35 mg (Once Weekly)
WEEK
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot#

Exp.

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one alendronate sodium tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one alendronate sodium tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* alendronate sodium tablets in the enclosed Patient Information leaflet. Please read it carefully.

Important information:
Please read the enclosed Patient Information leaflet before taking *Once Weekly* alendronate sodium tablets.
Keep this and all drugs out of the reach of children.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Lot XXXX
Exp XXXX

Mat. No. C22530

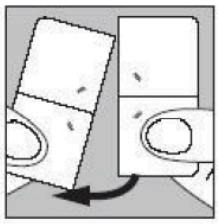
Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

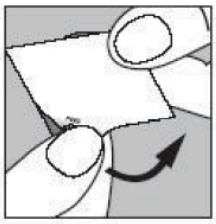
NDC 0093-5172-44
Once Weekly
Alendronate Sodium Tablets USP, 35 mg *
4 TABLETS

How to remove tablets:

1. Tear blister card at perforation.



2. Peel backing and push tablet through.



Apply Prescription Label Here

Mat. No. C22530

Iss. 12/2007

NDC 0093-5172-44

Once Weekly
ALENDRONATE SODIUM Tablets USP
35 mg*

35 mg Box - 4 Tablets Text
NDC 0093-**5172**-44
Once Weekly
ALENDRONATE SODIUM Tablets USP
35 mg*
For the prevention of osteoporosis in postmenopausal women
***Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).**
Osteoporosis is a disease that causes bones to become thin, weak, and easy to break.
That's why it is important you take *Once Weekly* alendronate sodium tablets to help protect your bones.
USUAL ADULT DOSAGE:
ONE 35 mg TABLET ONCE WEEKLY
See accompanying circular for complete dosage information.
Unit-of-Use dispense in original package.
Rx only
4 TABLETS
TEVA

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

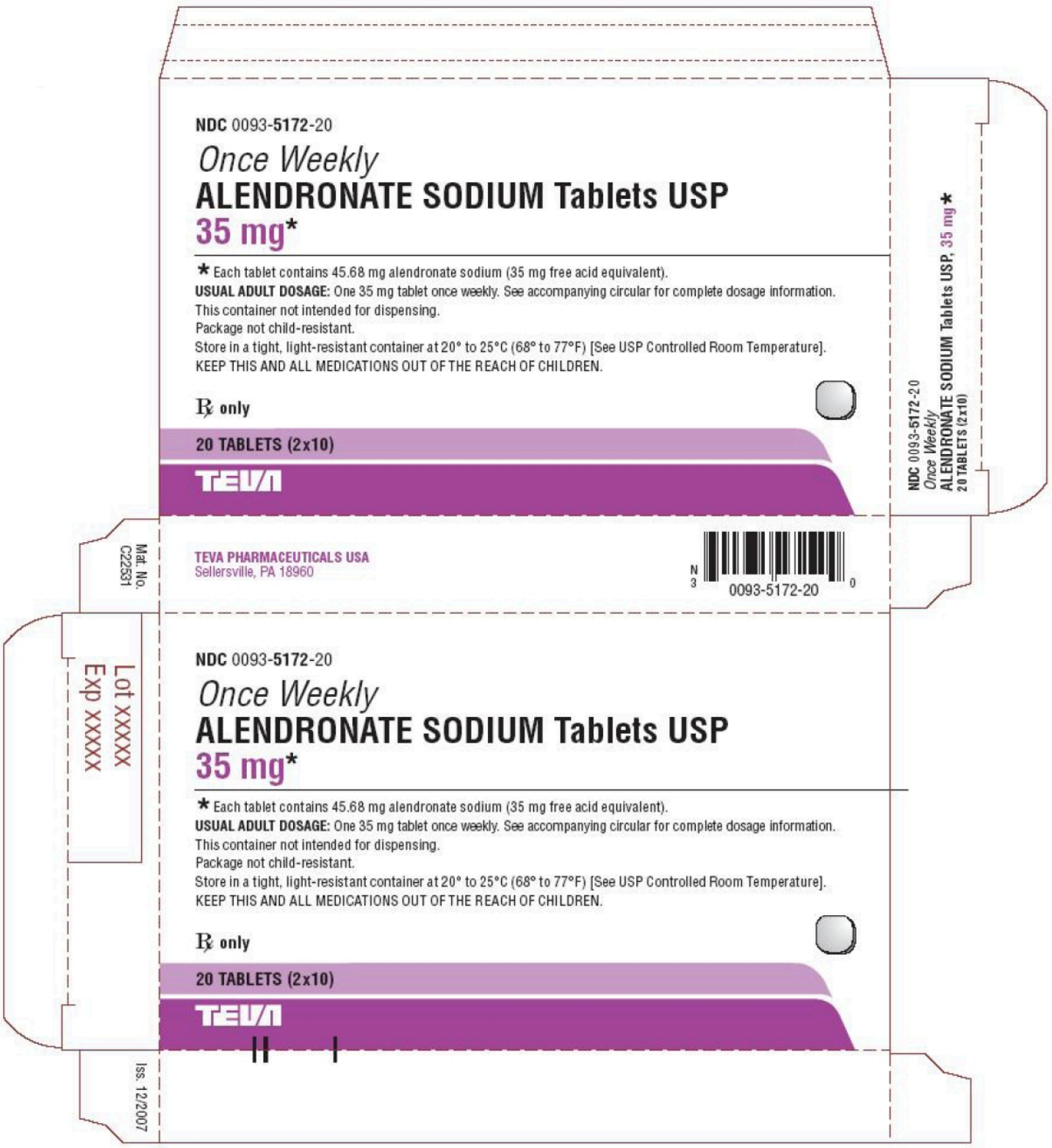
NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

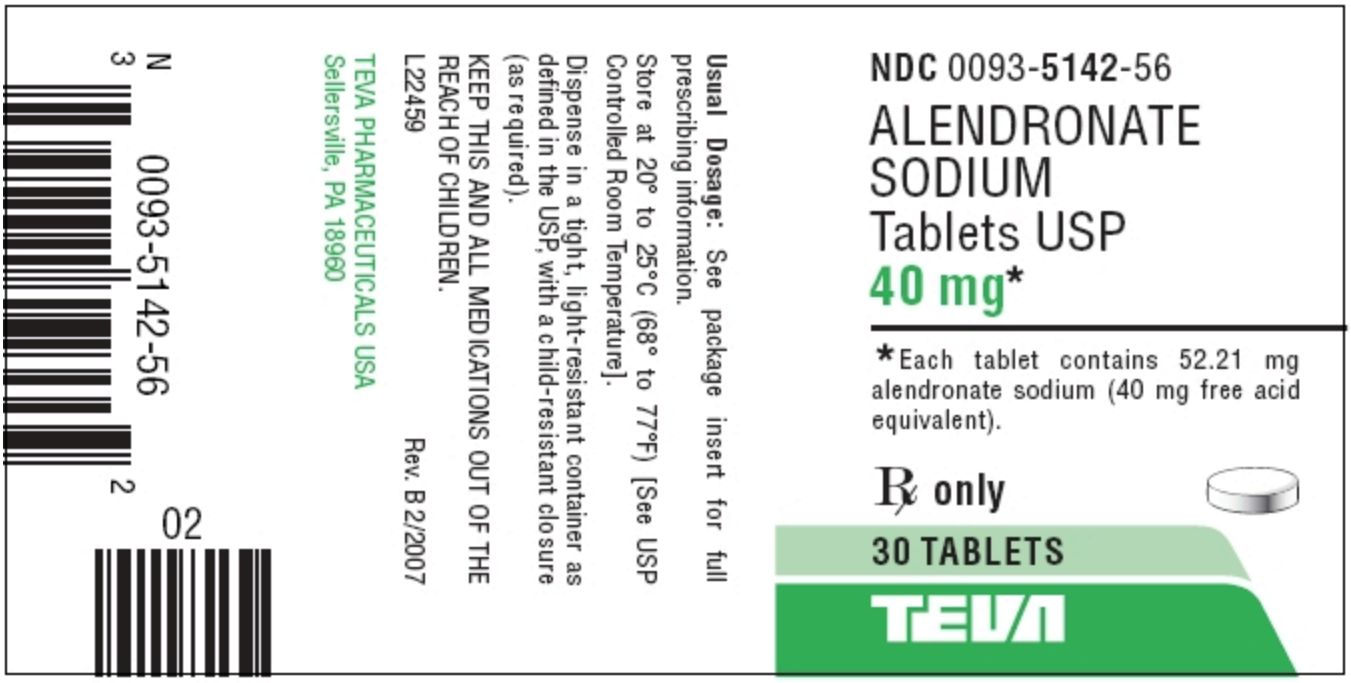
NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)00300935172194

35 mg Blister Card - 10 Tablets Text
NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.



35 mg Box - 20 Tablets Text
NDC 0093-**5172**-20
Once Weekly
ALENDRONATE SODIUM Tablets USP
35 mg*
***Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).**
USUAL ADULT DOSAGE: One 35 mg tablet once weekly. See accompanying circular for complete dosage information.
This container not intended for dispensing.
Package not child-resistant.
Store in a tight, light-resistant container at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Rx only
20 TABLETS (2 x 10)
TEVA



40 mg Label - 30 Tablets Text
NDC 0093-**5142**-56
ALENDRONATE
SODIUM
Tablets USP
40 mg*
***Each tablet contains 52.21 mg alendronate sodium (40 mg free acid equivalent).
Rx only
30 TABLETS
TEVA

70 mg Blister Card - 4 Tablets Text
NDC 0093-**5171**-19
ALENDRONATE
SODIUM Tablet USP
70 mg (Once Weekly)
WEEK
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot#
Exp.

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one alendronate sodium tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one alendronate sodium tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* alendronate sodium tablets in the enclosed Patient Information leaflet. Please read it carefully.

Important information:
Please read the enclosed Patient Information leaflet before taking *Once Weekly* alendronate sodium tablets.
Keep this and all drugs out of the reach of children.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Lot XXXXX
Exp XXXXX

Iss. 12/2007

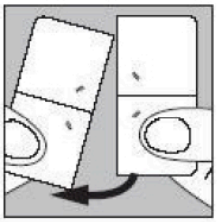
Mat. No. C22532

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

NDC 0093-5171-44
Once Weekly
Alendronate Sodium Tablets USP, 70 mg*
4 TABLETS

Apply Prescription Label Here

1. Tear blister card at perforation.
2. Peel backing and push tablet through.



How to remove tablets:

Iss. 12/2007

Mat. No. C22532

N 3 0093-5171-44 9

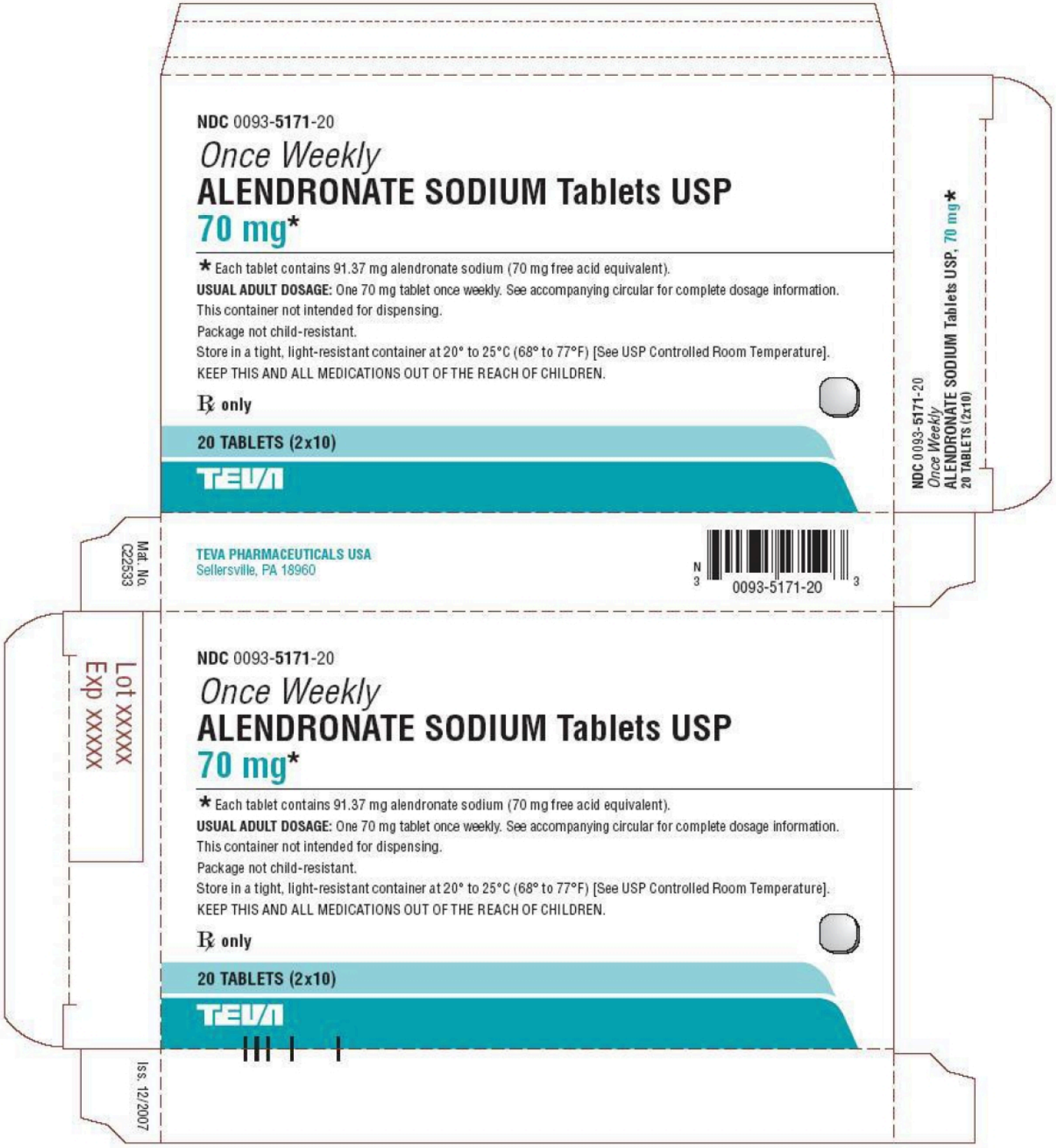
NDC 0093-5171-44

Once Weekly
ALENDRONATE SODIUM Tablets USP
70 mg*

70 mg Box - 4 Tablets Text
NDC 0093-**5171**-44
Once Weekly
ALENDRONATE SODIUM Tablets USP
70 mg*
For the treatment of osteoporosis in postmenopausal women
***Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).**
Osteoporosis is a disease that causes bones to become thin, weak, and easy to break.
That's why it is important you take *Once Weekly* alendronate sodium tablets to help protect your bones.
USUAL ADULT DOSAGE:
ONE 70 mg TABLET ONCE WEEKLY
See accompanying circular for complete dosage information.
Unit-of-Use dispense in original package.
Rx only
4 TABLETS
TEVA


NDC 0093-5171-19
Once Weekly
ALENDRONATE SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot#
Exp.
N(01)00300935171197

70 mg Blister Card - 10 Tablets Text
NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.



70 mg Box - 20 Tablets Text
NDC 0093-**5171-**20
Once Weekly
ALENDRONATE SODIUM Tablets USP
70 mg*
***Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).**
USUAL ADULT DOSAGE: One 70 mg tablet once weekly. See accompanying circular for complete dosage information.
This container not intended for dispensing.
Package not child-resistant.
Store in a tight, light-resistant container at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Rx only
20 TABLETS (2 x 10)
TEVA

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